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THE BOARD OF PATENT APPEALS AND INTERFERENCES



In re Application of
KRAEMER, et al

Application No.: **09/425,742**

Filed: **October 22, 1999**

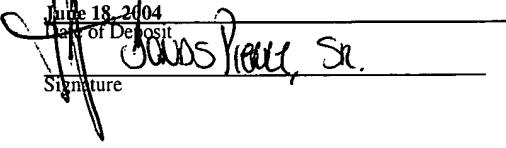
Title: **COMPOSITIONS FOR TOPICAL
APPLICATION HAVING
ANDROGENIC ACTIONS**

Examiner: **WELLS, Lauren Q.**

Art Unit: **1617**

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This is a reply to the Examiner's Answer dated April 20, 2004. The undersigned attorney believes that no fees are due for this submission. However, the Commissioner is authorized to charge any fees necessitated by this Reply Brief to Deposit Account No. 18-1982.

The purpose of this Reply Brief is to correct Counsel's statement of the real party in interest in the Appeal Brief filed December 15, 2003, to contest the Examiner's statement in the Examiner's Answer that all pending claims stand or fall together, and to address arguments made by the Examiner in the Examiner's Answer in support of the alleged motivation to combine the relied-on prior art.

REAL PARTY IN INTEREST

In addition to the Assignee, Aventis Pharma Deutschland GmbH, listed in the Appeal Brief as the real party in interest, the following parties may also be considered real parties in interest: ProSkelia S.A.S. of Romainville, France holds a license to this technology, and Inventors Karl T. Kraemer and Manfred Bohn may retain some rights to compensation under German inventorship laws if this application or a resulting patent are sold or commercialized.

GROUPING OF CLAIMS

The Examiner's statement on page 3 of the Examiner's Answer that "...claims 1-29 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof," is in error. The "Grouping of Claims" section of the Appeal Brief , page 5, states that claim 14 stands alone, claim 15 stands alone, claim 19 stands alone, claims 20 and 21 stand together, and claims 1-2, 4-8, 10-13, 16-17, 22-23, and 28-29 stand or fall together. Reasoned statements demonstrating why claims 14, 15, 19 and 20-21 stand or fall separately from the rest of the claims can be found on pages 16, 18, 19 and 20, respectively, of the Appeal Brief.

ARGUMENT

After the withdrawal of the 35 U.S.C. §112 rejection in the Examiner's Answer, all of the remaining rejections on appeal are 35 U.S.C. §103 rejections over a combination of references including Cretois (US 5,558,859) and Dubois (US 6,162,444). These §103 rejections are each improper because there is no motivation for one of skill in the art to combine the compositions of Formula I of the skin treatment of Dubois with the ceramide and/or glyceroceramide and at least one vinylpyrrolidone polymer of the hair or nail treatments of Cretois. These references teach compositions for treating entirely different tissues, and one of skill in the art would not consider components of the compositions readily interchangeable.

Applicants note that the Examiner seems to agree that one of skill in the art would not equate dermatological treatments with hair or nail treatments, because he has not argued so in any part of the instant, lengthy record. Instead, the Examiner has suggested the following three possible motivations: 1) both Cretois and Dubois teach treatments for the skin, so one of skill in the art would feel free to combine their components; 2) both Cretois and Dubois teach treatments for hair, so one of skill in the art would feel free to combine their components; or 3) the Dubois composition is taught to be an anti-seborrheic agent and one of skill in the art would be motivated to add that combination to the Cretois composition because Cretois suggests the addition of anti-seborrheic agents. Each of these alleged motivations is based on factually inaccurate readings of the prior art cited.

Cretois and Dubois do Not Both Teach Treatments for the Skin

The broadest disclosure of the tissue to be treated with Cretois' compositions is "the exoskeletal parts." See Abstract of Cretois. In the first paragraph of the specification of Cretois, this description is further refined to "keratinous exoskeletal parts". The Examiner has repeatedly grasped

the word “keratinous” from this definition to assert that, since skin contains keratin, Cretois teaches the treatment of skin. See, for example, the second full paragraph on page 9 of the Examiner’s Answer.

The Examiner ignores the fact that skin is not an “exoskeletal part.” Since Cretois contains no definition of “exoskeletal parts”, applicants submit the following two definitions of “exoskeleton”, both taken from current, well-known medical dictionaries, as demonstration that one of skill in the medical arts would understand that term to exclude vertebrate skin:

Exoskeleton 1. Hard parts, such as hair, teeth, nails, feathers, hooves, scales, etc., developed from the epidermis in vertebrates.

Stedman’s Medical Dictionary, 27th Edition, Lippincott Williams & Wilkins

Exoskeleton a hard structure developed on the outside of the body, as the shell of a crustacean. In vertebrates the term is applied to structures produced by the epidermis, as hair, nails, hoofs, teeth, etc.

Dorland’s Medical Dictionary, 27th Edition, W.B. Saunders Company

Copies of each definition are attached as an appendix to this Reply Brief. From these definitions, it is clear that one of skill in the medical arts would understand the “exoskeletal parts” of Cretois to be distinct from the skin (or epidermis). Although the epidermis and exoskeleton are linked by the fact that the exoskeleton is produced by the epidermis, the terms “epidermis” and “exoskeleton”, as used by those of skill in the medical arts, refer to distinct tissues.

Accordingly, the Examiner’s premise that both Cretois and Dubois teach preparations for treating skin is in error. Therefore, the motivation to combine Cretois and Dubois suggested by the Examiner, namely that one of skill in the art would freely combine components of compositions for treating the same tissues, is inapplicable to those references.

Cretois and Dubois do Not Both Teach Treatments for Hair

Dubois teaches a composition that contains “... a dermatologically effective amount of at least one liposome containing a compound of the formula ...”. See the abstract and column 1, lines 24-26. Accordingly, Dubois teaches compositions for use in treating the dermis, or skin. This is further pointed out in column 4, lines 42-49, which teaches that the compositions of Dubois become concentrated in the sebaceous glands of the epidermis.

However, the Examiner has repeatedly argued that since Dubois teaches “... the treatment of the epidermis for the conditions of hirsutism, androgenic alopecia and hyperilosity, which are all conditions of hair growth ...”, Dubois necessarily teaches the treatment of hair. {Please note the definitions of “exoskeleton” above, which show that hair is produced by, but a distinct tissue from,

the epidermis.} The Examiner reasons that Dubois' teaching of topical treatment of skin hair-growing must necessitate contact between the Dubois composition and any hair which grows from that skin area; "... it is impossible to apply a composition to the scalp without applying a composition to the hair." See the paragraph bridging pages 9 and 10 of the Examiner's Answer.

The Examiner's reasoning fails, because it stops there. The final step of the Examiner's proof is left as an unsupported assumption. It is certainly true that topical treatment of the scalp will necessarily lead to contact between the treating composition and hair in those the undersigned likes to refer to as "the hair fortunate". However, it is an unstated and unsupported assumption of the Examiner's reasoning that one of skill in the art would consider this inadvertent contact a treatment of those hair follicles. What pharmacological effect on the inadvertently contacted hair follicle is one of skill in the art supposed to infer from the "dermatologically effective" compound of Dubois that is taught to specifically concentrate in the sebaceous glands of the skin? While Dubois does lead to an inference of contact between the Dubois composition and hair, there is nothing in Dubois that supports the assumption that the Dubois composition is an effective treatment of the hair. If this line of reasoning were valid, wouldn't one of skill in the art necessarily conclude that chewable vitamins are, in fact, an effective topical treatment of the teeth? Applicants respectfully submit that one of skill in the cosmetic and dermatological arts would not conclude that chewable vitamins are a topical treatment of teeth or that the Dubois composition is an effective treatment for any tissue other than the epidermis.

Accordingly, the Examiner's premise that both Cretois and Dubois teach preparations for *treating* hair is in error. Therefore, the motivation to combine Cretois and Dubois suggested by the Examiner, namely that one of skill in the art would freely combine components of compositions for treating the same tissues, is inapplicable to those references.

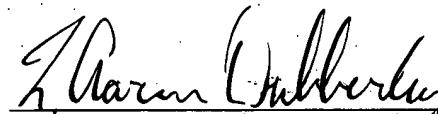
The Compounds of Formula I Taught by Dubois are Not Taught to be Anti-Seborrheic Agents

Cretois teaches at column 6, lines 36-44 that her compositions may additionally contain an antiseborrheic agent. The Examiner alleges that the last full paragraph of column 6 and the paragraph bridging columns 6 and 7 of Dubois can be interpreted to mean that the compounds of Dubois themselves are antiseborrheic agents and that one of skill would therefore be motivated to use the composition of Dubois as an additive to the Cretois composition. Applicants respectfully disagree with the Examiner's interpretation of those paragraphs in Dubois. As detailed in our Appeal Brief on pages 11 and 12, a more accurate reading of the combined disclosure of those two paragraphs is that only the addition of other anti-seborrheic compounds would enable use of the

Dubois composition as an anti-seborrheic agent. Accordingly, there is no motivation to combine the Dubois composition, as disclosed, with the composition of Cretois.

As shown above, none of the motivations alleged by the Examiner for one of skill in the art to combine the teachings Cretois and Dubois withstand scrutiny. Accordingly, the 35 U.S.C. §103 rejections based the combination of Cretois and Dubois must fall.

Respectfully submitted,



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Docket No.: DEAV1998/L071 US NP

STEDMAN'S Medical Dictionary

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exobi-*sh*ün-izm). A morbid compulsion to expose the body, especially the genitals, with the intent of arousing interest in the viewer.

exobi-*sh*ün-ist). One who engages in exhibitionism.

exhilarant). Mentally stimulating. [L. *ex-hilaro*, to gladden, to gladden]

existentialist). Pertaining to a branch of philosophy concerned with the search for the meaning of existence that has been extended into existential *psychopathology*, existence]

exit). An exit or outlet; death. [L. fr. *ex-eo*, pp. *-itus*, out]

Ernst (ek'st). Austrian physiologist, 1846-1926. SEE Call-E. [body; *E. plexus*]

exterior, or outward. SEE ALSO ecto-. [G. *exō*, outside]

extocardia (ek'so-kär'dē-ä). A glucanohydrolase acting on a linear end of the polysaccharide; e.g., β -amylase.

extocantigen (ek'so-an'ti-jen). SYN ectoantigen.

extocardia (ek'so-kär'dē-ä). SYN ectocardia.

exocrine (ek'so-krin). 1. Denoting glandular secretion delivered to a mucous or serous surface. SYN eccrine (1). 2. Denoting a gland that secretes outwardly through excretory ducts. [exo- + G. *krinō*, to secrete]

exocyclic (ek'si-klik, -sik'lik). Relating to atoms or groups in a cyclic structure but not themselves cyclic; e.g., the ring of toluene. Cf. endocyclic.

exocytosis (ek'so-si-to'sis). 1. The appearance of migrating cells in the epidermis. 2. The process whereby granules or droplets are released from a cell; the membrane of the granule fuses with the cell membrane, which then pinches off and the secretion is discharged. SYN exocytosis, emiocytosis, emiocytosis. [exo- + G. *kytos*, cell, + -osis, condition]

exophthalmia (ek'so-dē-vē-ä'shün). 1. SYN exophoria. 2. SYN exophthalmos.

exodontia (ek'so-don'shē-ä). The branch of dental practice dealing with extraction of teeth. [exo- + G. *odous*, tooth]

exodontist). One who specializes in the extraction of teeth.

exoenzyme (ek'so-en'zim). SYN extracellular enzyme.

exogamy (ek'so-gā'mē). Sexual reproduction by means of combining two gametes of different ancestry, as in certain protists. [exo- + G. *gamos*, marriage]

exogastrula (eks-ō-gas'tro-lä). An abnormal embryo in which the primitive gut has been everted.

exogenous (ek'so-jē-nē'ik). SYN exogenous.

exogen (ek'so-jē'nōt). In microbial genetics, the fragment of material that has been transferred from a donor to the recipient, being homologous for a region of the recipient's genome (endogenote), produces in the homologous region analogous to diploidy. [exo + genote]

exogenous (eks-ō-jē'nüs). Originating or produced outside of the body. SYN ectogenous, exogenetic. [exo- + G. *-gen*, condition]

exoglycosidase. A hydrolase removing terminal α -D-glucosidase residues from nonreducing ends of chains of β -D-glucose. SYN acid maltase, amyloglucosidase, glucoamylase.

exollevator (ek'so-lē'ver). A modified elevator for the extraction of teeth. [exo- + L. *levare*, to raise]

exomphalos (eks-om'fā-lōs). 1. Prominence of the umbilicus. SYN umbilical hernia. 2. SYN umbilical hernia. 3. SYN omphalocele, + *omphalos*, umbilicus

exon). A portion of a DNA that codes for a section of the messenger RNA from that DNA, and is therefore excreted (translated) into protein. [exo- + on]

ex-on shuf-fle. The variation in the patterns by which RNA may produce diverse sets of exons from a single gene.

exonuclease (ek-sō-noo'klē-äs). A nuclease that releases one nucleotide at a time, serially, beginning at one end of a polynucleotide (nucleic acid); several have been prepared from *Escherichia coli*, designated e. I, e. II, etc.; e. III, which removes nucleotides from 3' ends of DNA, is used in DNA sequencing. Cf. endonuclease.

exopeptidase (ek-sō-pep'ti-däs). An enzyme that catalyzes the hydrolysis of the terminal amino acid of a peptide chain; e.g., carboxypeptidase. Cf. endopeptidase.

Exophiala (ek-sō-fi'älä). A genus of pathogenic fungi having dematiaceous conidiophores with one- or two-celled annelloconidia. They cause mycetoma or phaeohyphomycosis; in cases of mycetoma, black granules develop in subcutaneous abscesses; in cases of phaeohyphomycosis, hyaline or brownish hyphae are found in tissues. [exo + G. *phiale*, a broad flat vessel]

E. jeansel'mei, a fungal species found in cases of mycetoma or phaeohyphomycosis.

E. werneckii, a fungal species that causes tinea nigra. SYN *Cladosporium werneckii*.

exophoria (ek'so-fō'rē-ä). Tendency of the eyes to deviate outward when fusion is suspended. SYN exodeviation (1). [exo- + G. *phora*, a carrying]

exophoric (ek-sō-fō'rīk). Relating to exophoria.

exophthalmic (ek-sof-thal'mik). Relating to exophthalmos; marked by prominence of the eyeball.

exophthalmometer (ek-sof-thal-mom'ē-ter). An instrument to measure the distance between the anterior pole of the eye and a fixed reference point, often the zygomatic bone. SYN orthometer, proptometer, statometer. [exophthalmos + G. *metron*, measure]

exophthalmos, exophthalmus (ek-sof-thal'mos). Protrusion of one or both eyeballs; can be congenital and familial, or due to pathology, such as a retroorbital tumor (usually unilateral) or thyroid disease (usually bilateral). SYN proptosis. [G. *ex*, out, + *ophthalmos*, eye]

endocrine e., e. associated with thyroid gland disorders. SEE Graves *ophthalmopathy*, Graves *orbitopathy*.

malignant e., relentless, progressive protrusion of the eyeballs.

exophyte (ek'sō-fit). An exterior or external plant parasite. [exo- + G. *phyton*, plant]

exophytic (ek-sō-fit'ik). 1. Pertaining to an exophyte. 2. Denoting a neoplasm or lesion that grows outward from an epithelial surface.

exoplasm (ek'sō-plazm). SYN ectoplasm.

exosero-sis (ek'sō-se-rō'sis). Serous exudation from the skin surface, as in eczema or abrasions.

exoskeleton (ek-sō-skel'ē-tōn). 1. Hard parts, such as hair, teeth, nails, feathers, hooves, scales, etc., developed from the epidermis in vertebrates. SYN dermoskeleton. 2. Outer chitinous envelope of an insect, or the chitinous or calcareous covering of certain Crustacea and other invertebrates.

exospore (ek'sō-spōr). An exogenous spore, not encased in a sporangium. [exo- + G. *sporos*, seed]

exosporium (ek-sō-spō'rē-um). The outer envelope of a spore.

exostectomy (ek-sos-tek'tō-mē). Removal of an exostosis. SYN exostosectomy. [exostosis + G. *ektomē*, excision]

exostosectomy (ek-sos-tō-sek'tō-mē). SYN exostectomy.

exostosis, pl. exostoses (eks-os-tō'sis, -sēz). A cartilage-capped bony projection arising from any bone that develops from cartilage. SEE ALSO osteochondroma. SYN hyperostosis (2), poroma (2). [exo- + G. *osteon*, bone, + -osis, condition]

e. bursa'ta, an e. arising from the joint surface of a bone and covered with cartilage and a synovial sac.

e. cartilagin'ea, an ossified chondroma arising from the epiphysis or joint surface of a bone.

hereditary multiple exostoses [MIM*133700], a disturbance of enchondral bone growth in which multiple, generally benign osteochondromas of long bones appear during childhood, commonly with shortening of the radius and fibula; the skull is not involved;

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in the epidermis as part of the inflammatory process.

exodeoxyribonuclease (ek'so-de-ok'se-ri'bo-nu'kle-äs) [EC 3.1.11.1] any of a sub-sub class of enzymes of the hydrolase class that catalyze the hydrolysis of terminal bonds of deoxyribonucleotides, releasing mononucleotides.

exodeviation (ek'so-de've-a'shun) 1. exophoria. 2. exotropia.

exodermic (ek'so-dér'mik) [ex- + Gr. *hodos* way] centrifugal or effluent.

exodontia (ek'so-don'she-ah) exodontics.

exodontics (ek'so-don'tiks) that branch of dentistry dealing with extraction of the teeth. Called also *exodontia*.

exodontist (ek'so-don'tist) a dentist who practices exodontics.

exoenzyme (ek'so-en'zim) an extracellular enzyme; an enzyme that acts outside of the cells in which it originates.

exoergic (ek'so-er'jik) characterized by or accompanied by loss of free energy; releasing energy, as in a chemical reaction during and by which energy is released; energy releasing. Cf. *endoergic* and *endothermic*.

exoerythrocytic (ek'so-ë-rith'ro-si'tik) outside the erythrocyte, a term applied to stages in the development of malarial parasites which takes place in tissue cells instead of in erythrocytes.

exogamy (ek-sog'ah-me) [exo- + Gr. *gamos* marriage] procreation/fertilization by the union of elements that are not derived from the same cell. Cf. *autogamy* (def. 1) and *endogamy* (def. 1).

exogastric (ek'so-gas'trik) pertaining to the external surface of the stomach.

exogastritis (ek'so-gas-tri'tis) inflammation of the external coat of the stomach.

exogastrula (ek'so-gas'troo-lah) [exo- + *gastrula*] a gastrula in which invagination is hindered and the mesentoderm bulges outward.

exogastrulation (eks'o-gas'troo-la'shun) the evagination to the exterior (or turning inside out) of the gut due to an interference with the normal processes of gastrulation, which can occur if the morula is cut transversely below the equator. It is usually followed by a migration of mesenchyme cells into the interior.

exogemmina (ek'so-jem'mi-nah) [exo- + *gemmare* to bud] a suborder of endocommensal ciliate, mostly stalked protozoa (order Chonotrichida, superorder Phyllopharyngida) found in fresh and brackish waters. They reproduce by external budding and have a relatively large, long cylindrical body with a well-developed collar.

exogenetic (ek'so-jé-net'ik) [exo- + Gr. *gennan* to produce] exogenous.

exogenic (ek'so-jen'ik) exogenous.

exogenina (ek'so-jé-ni'ah) [exo- + Gr. *gennan* to produce] a suborder of ciliate protozoa (order Suctorida, subclass Suctoria), most species of which are large and either solitary and marine, free-living, or endocommensal organisms, and some species have both prehensile and suctorial tentacles; the larvae of some species are long, vermiform, nonmotile, and practically naked. The organisms reproduce by exogenous budding without invagination of the parental cortex.

exogenote (eks'o-je'nöt) in bacterial genetics, the extra piece of genetic information introduced by transduction into the recipient cell by the donor cell. Cf. *endogenote*.

exogenous (eks'o-ë-nüs) [exo- + Gr. *gennan* to produce] developed or originating outside the organism, as exogenous disease. 2. growing by additions to the outside.

exognathia (ek'sog-na'the-ah) prognathism.

exognathion (ek'sog-na'the-on) [exo- + Gr. *gnathos* jaw] the maxilla exclusive of the premaxilla.

exomphalos (eks-om'fah-lös) [ex- + Gr. *omphalos* navel] congenital umbilical hernia.

exomysium (eks'o-mi'se-um) perimysium.

exon (eks'on) a coding sequence in a gene; see *intron*.

exonuclease (ek'so-nu'kle-äs) [EC 3.1.11.16] any of the enzymes of the hydrolase class that catalyze the hydrolysis of terminal bonds of deoxyribonucleotide or ribonucleotide chains, releasing mononucleotides. Cf. *endonuclease*.

exopathic (ek'so-path'ik) of the nature of an exopathy; originating outside the body.

exopathy (eks-op'ah-the) [exo- + Gr. *pathos* disease] a disease originating in some cause lying outside the organism; exogenous disease.

exopeptidase (ek'so-pep'ti-däs) any enzyme of the hydrolase class that catalyzes the hydrolysis of a terminal peptide bond, releasing a single amino acid from that chain.

exophoria (ek'so-fo're-ah) [exo- + *phoria*] a form of heterophoria in which there is deviation of the visual axis of one eye away from that of the other eye in the absence of visual fusional stimuli. Called also *exodeviation*.

exophoric (ek'so-for'ik) pertaining to or characterized by exophoria.

exophthalmic (ek'so-thal'mik) of or pertaining to or characterized by exophthalmos.

exophthalmogenic (ek'so-thal'mo-jen'ik) causing or producing exophthalmos.

exophthalmometer (ek'so-thal'mom'ë-ter) an instrument for measuring the amount of exophthalmos; called also *ophthalmostatometer*, *orthometer*, *proptometer*, *protometer*, and *stomatometer*.

exophthalmometric (ek'so-thal'mo-met'rik) pertaining to exophthalmometry.

exophthalmometry (ek'so-thal'mom'ë-tre) [exophthalmos + -metry] measurement of the extent of protrusion of the eyeball in exophthalmos.

exophthalmos (ek'so-thal'mos) [exo- + Gr. *ophthalmos* eye] abnormal protrusion of the eyeball; called also *proptosis*.

endocrine e., exophthalmos associated with disorder of an endocrine gland, commonly thyrotoxicosis. **malignant** e., the severe exophthalmos of Graves' disease in which there is marked edema and infiltration of the orbital tissues and extraocular muscles, proptosis, and stare. It was formerly attributed to overactivity of thyrotropin, and so was formerly called *thyrotropic* e. **pulsating** e., exophthalmos with pulsation and bruit, often due to aneurysm pushing the eye forward. **thyrotoxic** e., a mild form due to thyrotoxicosis. **thyrotropic** e., malignant e.

exophthalmus (ek'so-thal'mus) exophthalmos.

exophytic (ek'so-fit'ik) [exo- + Gr. *phyein* to grow] growing outward; in oncology, proliferating on the exterior or surface epithelium of an organ or other structure, in which the growth originated.

exoplasm (ek'so-plazm) plasma membrane.

exorbitism (ek-sor'bë-tizm) exophthalmos.

exoribonuclease (ek'so-ri'bo-nu'kle-äs) [EC 3.1.13-14] any enzyme of two sub-subclasses of the hydrolase class that catalyzes the hydrolysis of terminal bonds of ribonucleotides, producing mononucleotides.

exosepsis (ek'so-sep'sis) [exo- + Gr. *sépsis* decay] septic poisoning which does not originate within the organism.

exoserosis (ek'so-se-ro'sis) an oozing of serum or exudate, as in moist skin diseases and edema.

exoskeleton (ek'so-skel'ë-ton) [exo- + *skeleton*] a hard structure developed on the outside of the body, as the shell of a crustacean. In vertebrates the term is applied to structures produced by the epidermis, as hair, nails, hoofs, teeth, etc.

exosmose (ek'sos-mös) to diffuse from within outward.

exosmosis (ek'sos-mo'sis) [exo- + Gr. *osmos* impulsion] diffusion or osmosis from within outward; movement outward through a diaphragm or through vessel walls. Cf. *endosmosis*.

exospore (ek'so-spör) conidium.

exosporium (ek'so-spo're-um) the external layer of the envelope of a spore.

exostosectomy (ek-sos'to-sek'to-me) excision of an exostosis.

exostosis (ek'sos-to'sis) [exo- + Gr. *osteon* bone] a benign bony growth projecting outward from the surface of a bone, characteristically capped by cartilage. **e. bursa'ta**, an exostosis from the epiphyseal portion of a bone, consisting of bone and cartilaginous tissue covered by a connective-tissue capsule.

e. cartilagin'ea, a variety of osteoma consisting of a layer of cartilage developing beneath the periosteum of a bone. **hereditary multiple exostoses**, multiple **e. ivory e.**, a bony growth of great density. **multiple exostoses**, a hereditary disorder characterized by exostoses near the extremities of diaphyses of long bones, which may